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Glucocerebrosidase deficits in sporadic Parkinson disease

Karen E Murphy and Glenda M Halliday*

Neuroscience Research Australia; School of Medical Sciences; Faculty of Medicine; University of New South Wales; Sydney, Australia

Parkinson disease (PD) is a progressive neurodegenerative movement disorder characterized pathologically by abnormal SNCA/α-synuclein protein inclusions in neurons. Impaired lysosomal autophagic degradation of cellular proteins is implicated in PD pathogenesis and progression. Heterozygous *GBA* mutations, encoding lysosomal GBA/glucocerebrosidase (glucosidase, β, acid), are the greatest genetic risk factor for PD, and reduced GBA and SNCA accumulation are related in PD models. Here we review our recent human brain tissue study demonstrating that GBA deficits in sporadic PD are related to the early accumulation of SNCA, and dysregulation of chaperone-mediated autophagy (CMA) pathways and lipid metabolism.

Keywords: Parkinson disease, α-synuclein, glucocerebrosidase, autophagy, chaperone-mediated autophagy, lysosomes, ceramide

Abbreviations: CMA, chaperone-mediated autophagy; GBA, glucosidase, beta, acid; PD, Parkinson disease

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*Correspondence to: Glenda M Halliday; Email: g.halliday@neura.edu.au

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Gaucher disease is a lysosomal storage disorder caused by homozygous mutations in *GBA*, where loss of functional GBA enzyme activity results in abnormal lipid accumulation. Families with Gaucher disease have an increased incidence of PD, and heterozygous *GBA* mutations are the most common genetic risk factor for PD (4–7%). PD is characterized by the abnormal neuronal accumulation of SNCA into insoluble aggregates called Lewy bodies. SNCA is degraded primarily through lysosomal autophagic pathways, which are impaired in PD. Recent in vitro studies suggest a detrimental reciprocal relationship between wild-type SNCA and GBA, while reduced levels of GBA protein and enzyme activity are reported in affected brain regions in PD patients with and without *GBA* mutations.

Our recent study used post-mortem brain tissue to determine if early pathological SNCA abnormalities directly relate to GBA deficiencies or to other lysosomal, autophagic, and sphingolipid abnormalities in sporadic PD without *GBA* mutations. Specificity and timing of these relationships was determined by the use of 2 brain regions—one with pathological SNCA (anterior cingulate cortex) and one without (occipital cortex)—and patients at the earliest (Braak stage IV) or later stages of PD. This study design confirmed that largely biochemical SNCA changes occur first in regions with limited pathology and neuron loss compared with subsequent structural degenerative changes.

GBA protein levels and enzyme activity are selectively reduced and relate to increased levels of SNCA in early stage PD. GBA levels do not differ between early and later stages of PD. Reduced *GBA* mRNA expression is found in both regions and also does not differ between early and later stages of PD, suggesting that cells can tolerate reduced *GBA* mRNA without significantly compromising GBA enzyme activity. Collectively, these results suggest that GBA deficiencies occur early and are related to pathological PD tissue changes.

Next we determined that these GBA deficits are not simply due to reduced numbers of lysosomes, as the levels of constituent lysosomal membrane proteins (LAMP1, LAMP3, and SCARB2/LIMP2) and a lysosomal hydrolase (CTSK/cathepsin K) are not altered in early stage PD, and are unchanged at later stages. These data also confirm that the PD GBA deficiency is not due to reduced

levels of the GBA ER-lysosome trafficking receptor SCARB2.

There is a selective reduction in LAMP2 and selective increases in CTSA and CTSD early in PD, with no further change at later stages. Reduced LAMP2 levels are related to both increased SNCA and reduced GBA enzyme activity, whereas the increased cathepsins were not. A portion of SNCA is degraded through CMA, where LAMP2A is the CMA membrane receptor and rate-limiting factor, CTSA is involved in the regulation of LAMP2A degradation, and CTSD is the primary lysosomal enzyme responsible for SNCA degradation. Collectively, our data indicate an early selective nonprogressive dysfunction in the lysosomal CMA system in sporadic PD, with early GBA deficits more related to membrane interactions than to lysosomal hydrolase dysregulation. Increased CTSA and reduced LAMP2 support a scenario where early dysregulation of CMA occurs in sporadic PD through increased degradation of LAMP2A, resulting in reduced CMA and buildup of CMA-degraded cellular proteins including SNCA.

Chronic reductions in CMA can activate macroautophagy; however, we did not observe any change in levels of the autophagosome protein LC3-II in early or later stage PD, suggesting no change in steady-state levels of autophagosome number, but not eliminating the possibility of alterations in autophagic flux. BECN1, also required for autophagosome formation, was selectively reduced in early stage PD, a change related to reduced GBA protein but not to increased SNCA. BECN1 is also implicated in regulation of retrograde endosomal transport, and dysfunctional retromer complex-mediated endosomal-Golgi trafficking has been recently linked to 3 PD susceptibility genes (*LRRK2*, *PARK16/RAB7L1*, and *VPS35*). We speculate that the associated BECN1 and GBA deficits in early PD may link *GBA* to this PD-related pathway rather than to macroautophagy deficits.

Lipid accumulation within lysosomes is the major pathological finding in Gaucher disease. Our lipidomics analysis identified a reduction in ceramide but not sphingomyelin in brain regions with SNCA accumulation and GBA deficiency in sporadic PD. The ceramide salvage pathway (dependent on lysosomal GBA) is considered the most energy-efficient mechanism of ceramide generation in neurons, so decreased ceramide early in PD may suggest that impairment of the salvage pathway is not compensated for by upregulation of de novo ceramide synthesis. Such sphingolipid changes may have an impact on cellular membrane structure and signaling pathways, suggesting significant changes in neuronal membrane properties in PD.

This study demonstrated that wild-type GBA levels and activity correlate with pathological changes in SNCA early in PD. This early GBA deficit is not due to loss of neurons or lysosomes, and corresponds to reduced CMA but not macroautophagy, increased SNCA, and decreased ceramide. These abnormalities were not progressively worse at later PD stages, suggesting that lysosomal dysfunction occurs early within surviving neurons and, while substantial, is insufficient to immediately induce cell death. Reduced GBA levels alone are insufficient to cause PD, as only a small percentage of *GBA* mutation carriers develop PD. We speculate that the early increase in SNCA may initiate loss of GBA enzyme activity in sporadic PD, with neuronal GBA deficits contributing to early lysosomal dysfunction by altering lysosomal membrane properties and precipitating a redistribution of cellular membrane proteins. Chronic lysosomal dysfunction over the course of PD supports a role for lysosomal membrane destabilization in the neurodegeneration found at later stages.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.